matter. Applicants cancel, without prejudice, claim 24. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the Group and/or Art Unit of this application has changed. Applicants will address this and all future correspondence to Regina M. DeBerry, Group Art Unit 1647.

The Examiner has stated that the priority claim in this application has not been perfected, and accordingly, Applicants are not entitled to claim priority from Provisional Application No. 60/058,258, filed September 9, 1997. In addition, the Examiner has made other formal objections to the specification. Applicants have attended to the Examiner's objections to the specification. Reconsideration and withdrawal are requested.

a. The specification has now been amended to make specific reference to both the PCT application and the prior provisional application. As a result of this amendment, the effective filing date of the present application is September 9, 1997.

b. An Abstract for this application has been added.

c. The Brief Description of the Drawings has been amended in order to provide an appropriate description for FIGS. 1A and 1B.

d. Claims 11, 13, 18, 19 and 23 have been amended to remove certain informalities as noted in the Office Action.

Claims 1, 11, 13, and 15-24 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To expedite prosecution, Applicants have amended the claims to more explicitly point out the claimed OP/BMP morphogens used in the methods of the present invention. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

The Examiner states that the present claims are open to include a large number of possible amino acid sequence variants, and that these variants may not be operable in the context of the invention. However, applicants respectfully submit that simply because a claim is open to include a large number of possible embodiments does not mean that the claim is overly broad or not enabled. The test for enablement is whether one of skill in the art could practice the claimed invention without undue experimentation. In other words, whether the claim is supported by the specification. No objection has been made that the claims lack support in the specification. Moreover, a limited amount of experimentation is permissible under 35 U.S.C. 112, first paragraph, to determine whether a particular variant is operable. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

The morphogens used in the methods of the present invention are described based on both their sequence, as well as on a functional limitation. Accordingly, one of skill in the art can readily envision the claimed subject matter. Applicants direct the Examiner's attention to page 11, lines 1-9 and page 11, line 30-page 12, line 9 which provide methods to align OP/BMP morphogens, as well as specific assays to evaluate the function of morphogens and morphogen variants.

> "As will be understood by those skilled in the art, homologous or functionally equivalent sequences include functionally equivalent arrangements of the cysteine residues within the conserved cysteine skeleton, including amino acid insertions or deletions which alter the linear arrangement of these cysteines, but do not materially impact their relationship in the folded structure of the dimeric protein, including their ability to form such intra- or inter-chain disulfide bonds as may be necessary for biological activity." (page 11, lines 4-9).

> "[C]onservative amino acid substitutions are residues that are physically or functionally similar to the corresponding reference residues, having similar size, shape, electric charge, and/or chemical properties such as the ability to form covalent or hydrogen bonds, or the like." (page 11, lines 19-21).

Armed with the extensive guidance provided in the specification regarding the structure and function of the morphogens for use in the methods of the present invention, the only remaining question is whether the construction and testing of said morphogens constitutes undue experimentation. Applicants contend that such experimentation, though possibly time-consuming, is routinely practiced in the art and is not undue. Although Applicants provided considerable information to one of skill in the art regarding the construction of polypeptide variants, the art at the time of filing no longer relied upon purely rational choices of conserved amino acid substitutions to construct polypeptide variants. The fields of combinatorial and scanning mutagenesis had trivialized the once complex and painstaking process of making and testing polypeptide variants long before the filing of the present application (for examples see Reidhaar-Olson and Sauer, 1988; Wissmann et al., 1991; Delagrave et al., 1993; enclosed herewith as Exhibits 1-3). These techniques were routinely practiced, and allow a wide range of amino acid substitutions to be made and tested for the maintenance or disruption of functional properties without undue experimentation. Although the specification may not provide extensive guidance on the use of combinatorial mutagenesis, MPEP 2164.05(a) makes clear that the "specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*". Such is the case here. Techniques for synthesizing, testing and identifying sequences which would possess the recited structures and functions were well known in the art at the time of filing and routinely carried out. Accordingly, one of skill in the art faced with the task of constructing and identifying morphogens which meet the functional limitations of the pending claims would not expect to expend any more effort than normally required.

Accordingly, in Applicants' view, the scope of the present claims fully satisfies the enablement requirement of 35 U.S.C. 112, first paragraph. Additionally, Applicants direct the Examiner's attention to a variety of references published both before and since the filing of the current application which demonstrate that morphogens according to the present invention induce ectopic bone (Wang et al., 1990; Aono et al., 1995; Musgrave et al., 1999; Zhu et al., 1999; Nakagawa et al., 2001, enclosed herewith as Exhibits 4-8). Accordingly, one of skill in the art can readily utilize the disclosed ectopic bone assay to determine the OP/BMP morphogens for use in the methods of the present invention.

Applicants additionally note that the overlapping activity among OP/BMP family members is not limited to bone formation. The present invention is directed to the use of OP/BMP morphogens in neural tissue, and the specification provides experimental evidence supporting the role of OP-1 in neural growth and survival. Applicants additionally direct the Examiner's attention to Charytoniuk et al. which demonstrate that several OP/BMP family members are expressed in both the developing and the adult rat brain (Charytoniuk et al., 2000, enclosed herewith as Exhibit 9). Charytoniuk et al. also demonstrate that BMP receptors are expressed in the brain consistent with the responsiveness of these cells to BMP signaling. RT-PCR analysis reveals that BMPR-IA and BMPR-II, as well as the morphogens BMP2, BMP3, BMP4, BMP5, BMP6, and BMP7 are expressed in the adult rodent brain (Charytoniuk et al., page 34, Figure 1). In view of the experimental evidence provided by Applicants, as well as post-filing evidence which indicates that other OP/BMP family members and their receptors are expressed in the developing and adult brain, one of skill in the art would reasonably expect that a wide variety disparate OP/BMP morphogens meeting the limitations explicitly stated in the claims can be used in the subject methods. Accordingly, Applicants contend that the claims are enabled throughout their scope.

The OP/BMP morphogens for use in the claimed methods are described based on structural, as well as functional criteria. Additionally, the specification and the state of the art provide methods for readily making variants which meet the structural limitations of the claims. These methods make the actual construction of the polypeptides routine. Furthermore, the specification and the state of the art provide assays with which to readily evaluate whether the OP/BMP morphogens meet the functional limitations set forth in the claims. Accordingly, the experimentation required to make and test OP/BMP morphogens for use in the claimed methods is not undue, and the claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection are requested.

Furthermore, claim 24 was rejected under 35 U.S.C. 112, first paragraph. To expedite prosecution, Applicants have canceled claim 24 rendering rejection of this claim moot. Cancellation of claim 24 is not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Claims 28 and 29 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement in the specification. The Examiner has stated that these claims, which are drawn to pharmaceutical preparations, are not enabled since the specification is only enabling for *in vitro* processes. This ground of rejection is traversed.

Applicants acknowledge that there is a difference between *in vivo* and *in vitro* methods. However, the Examiner fails to acknowledge that the purpose of *in vitro* experimentation is to model or simulate how a particular treatment protocol would function in an *in vivo* model. In the case of the present invention, there is no sound reason to question that the claimed treatment methods would be efficacious in an *in vivo* model. For instance, pages 18-21 of the specification set forth typical pharmaceutical formulations and routes of administration which would be operable in the present invention.

Additionally, Applicants have provided extensive evidence in a neuronal culture system to support the enablement of the scope of the present claims. In accordance with MPEP 2164.02, the establishment of strong in vitro evidence or in vivo evidence obtained in a non-human animal model system is sufficient to make a correlative argument for a claimed in vivo method. "An in vitro or in vivo animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." Applicants have presented evidence which demonstrates that the methods of the present invention have broad applicability. Applicants demonstrate the synergistic effects of administering a combination of OP/BMP morphogens and GDNF/NGF neurotrophic factors to tissues derived from several different regions including the lumbar region, the lumbar-sacral region, the orbit, and the dorsal mesorectum. Accordingly, one of skill in the art would reasonably correlate this data with the general ability of this combination to function in other models. Such correlation need not be exact or rigorous, as asserted by Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir. 1985). "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

Applicants have demonstrated the efficacy of the invention in several model culture system. Applicants cannot be expected to wait for additional laboratory models to spontaneously develop. This sentiment was echoed by the Federal Circuit in In *re* Brana. In addressing whether the invention satisfied the utility requirement, the Court found that the applicants' experimental evidence in a particular tumor model was sufficient evidence of the utility of the invention. Furthermore, the Court pointed out that if scientists were required to wait until animal models for all diseases were developed or occurred spontaneously, there would be no effective way to conduct medical experiments. "If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo*, as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale." (In *re* Brana, 51 F.3d 1560, 34 USPQ2d 1436 Fed Cir. 1995). Accordingly, reconsideration and withdrawal are requested.

Claims 1, 11, 13, and 15-24 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by the Bengtsson et al. reference. Applicants traverse the rejection.

Without reviewing the merits of the Bengtsson reference in detail, applicants observe that the effective date of this reference appears to be May 19, 1998, based on the date of acceptance of the paper. However, applicants intend to perfect the priority claim for the provisional application which the present application is based on. After perfecting the priority claim, the effective date of this application will be September 9, 1997. Consequently, the rejection on the basis of this reference will be effectively obviated.

Claims 1, 11, 13 and 15-24 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over the Lein et al. reference in view of the Durbec et al. reference. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as obvious over the Lein et al. reference in view of Durbec et al. and Weiss et al. These grounds of rejection are respectfully traversed.

The Examiner contends that Lein et al. discloses that OP-1 and NGF are cofactors that influence dendritic growth in sympathetic neurons. The Examiner also acknowledges that Lein et al. is directed exclusively to NGF, and is silent on other nerve growth factors, such as GDNF. In

order to remedy the shortcomings of the Lein et al. reference, the Examiner has cited the Durbec et al. reference as disclosing the functional interaction between the Ret receptor and GDNF. However, Durbec et al. does not teach or suggest any equivalence between NGF and GDNF as contended by the Examiner. Nor does the Examiner cite any other evidence in the art to establish a structural equivalence between GDNF and NGF.

In particular, Durbec et al. discloses that GDNF has unique properties among nerve factors in that it signals through Ret RTK, and is a distant member of the TGF-β superfamily. The reference highlights this uniqueness by emphasizing that GDNF signals through an RTK, while other members of the TGF-β superfamily signal through serine-threonine kinase receptors. See pages 791 and 792 of the reference. In contrast, as explicitly pointed out in the specification, NGF is a member of the neurotrophin family. Consequently, there is no basis for concluding that one skilled in the art would be motivated to combine the Lein et al. and Durbec et al. references as suggested by the Examiner. In light of both the specification and the knowledge in the art with respect to growth factors, GDNF and NGF are growth factors belonging to separate families. Accordingly, there is no motivation to combine the cited references. Reconsideration and withdrawal of this rejection is requested.

The Weiss et al. reference discloses the preparation of pharmaceutical compositions which include various ingredients, including morphogens. However, this reference does not cure the deficiencies of the Lein et al. and Durbec et al. references as noted earlier, as applied to claims 28 and 29. Reconsideration and withdrawal of this reference is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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